University of Glasgow

Cunningham, J. W. et al. (2020) Natriuretic peptide-based inclusion criteria in a heart failure clinical trial: insights from COMMANDER HF. *JACC: Heart Failure*, 8(5), pp. 359-368. (doi: 10.1016/j.jchf.2019.12.009).

This is the author's final accepted version.

There may be differences between this version and the published version. You are advised to consult the publisher's version if you wish to cite from it.

http://eprints.gla.ac.uk/214074/

Deposited on: 20 April 2020

Enlighten – Research publications by members of the University of Glasgow
http://eprints.gla.ac.uk

Title: Natriuretic Peptide-Based Inclusion Criteria in a Heart Failure Clinical Trial: Insights from COMMANDER HF

Short Title: COMMANDER HF Natriuretic Peptides

Jonathan W. Cunningham, M.D.,[a]* João Pedro Ferreira, M.D., Ph.D.,[b]* Hsiaowei Deng, M.S.,[c] Stefan D. Anker,[d] M.D., Ph.D., William M. Byra, M.D.,[c] John G.F. Cleland, M.D., FACC,[e] Mihai Gheorghiade, M.D., FACC, [d]** Carolyn S.P. Lam, M.D., Ph.D., FACC,[g] David La Police,[c] Mandeep R. Mehra, M.D., FACC,[a] James D. Neaton, Ph.D.,[h] Theodore E. Spiro, M.D.,[i] Dirk J. van Veldhuisen, M.D., Ph.D., FACC,[j] Barry Greenberg, M.D., FACC,[k] and Faiez Zannad, M.D., Ph.D. [b]

[a] Brigham and Women's Hospital and Harvard Medical School, Boston, MA
[b] Centre d'Investigations Cliniques-Plurithématique 1433, and INSERM U1116, CHRU, F-CRIN INI-CRCT (Cardiovascular and Renal Clinical Trialists), Nancy, France
[c] Janssen Research & Development, Raritan, NJ
[d] Department of Cardiology (CVK); and Berlin Institute of Health Center for Regenerative Therapies (BCRT); German Centre for Cardiovascular Research (DZHK) partner site Berlin; Charité Universitätsmedizin Berlin, Germany
[e] Robertson Centre for Biostatistics & Clinical Trials, University of Glasgow, and National Heart & Lung Institute, Imperial College London, United Kingdom
[f] Northwestern University, Chicago, IL
[g] National Heart Centre Singapore and Duke-–National University of Singapore, Singapore; Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands; The George Institute for Global Health, Australia
[h] Division of Biostatistics, School of Public Health, University of Minnesota, Minneapolis, MN
[i] Bayer HealthCare Pharmaceuticals, Whippany, NJ
[j] Department of Cardiology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands
[k] Department of Medicine, Cardiology Division, University of California, San Diego, CA
* Drs. Cunningham and Ferreira are joint first authors
** Deceased

Word Count: 4,258

Twitter handle: @JonWCunningham
Tweet summary: COMMANDER-HF: Natriuretic peptide inclusion criteria increase event rates, should be standard for future HF trials

Corresponding Author:
Faiez Zannad MD PhD
Professor of Therapeutics and Cardiology

Director of Clinical Investigation
CIC Inserm, Institut Lorrain du Coeur et des Vaisseaux
CHU de Nancy
54500 Vandoeuvre lès Nancy, France
f.zannad@chru-nancy.fr

Funding & Disclosures:

Funding: The COMMANDER HF trial was sponsored by Janssen Research and Development.

Relationships to Industry: Dr. Cunningham is supported by the National Heart, Lung, and Blood Institute T32 postdoctoral training grant (T32HL094301-10). Dr. Anker has received grant support from Abbott Vascular, grant support and personal fees from Vifor, and personal fees from Janssen, Servier, Bayer, Boehringer Ingelheim, Respicardia, Impulse Dynamics and Novartis. Dr. Cleland reports personal fees from Janssen Research & Development LLC as a member of the steering committee of the COMMANDER HF trial and research grants and honoraria for speaking, committees, and advisory boards from Amgen, AstraZeneca, Bayer, Bristol-Myers Squibb, GlaxoSmithKline, Johnson & Johnson, Medtronic, MyoKardia, Novartis, Philips Healthcare, Pharmacosmos, Pharma Nord, Sanofi, Laboratoires Servier, Stealth BioTherapeutics, Torrent Pharmaceuticals, and Vifor Pharma. Dr. Lam is supported by a Clinician Scientist Award from the National Medical Research Council of Singapore; has received research support from Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, and Vifor Pharma; has served as consultant or on the Advisory Board/ Steering Committee/ Executive Committee for Boston Scientific, Bayer, Roche Diagnostics, AstraZeneca, Medtronic, Vifor Pharma, Novartis, Amgen, Merck, Janssen Research & Development LLC, Menarini, Boehringer Ingelheim, Novo Nordisk, Abbott Diagnostics, Corvia, Stealth BioTherapeutics, JanaCare, Biofourmis, Darma, Applied Therapeutics, MyoKardia, WebMD Global LLC, Radcliffe Group Ltd and Corpus. Mr. La Police, Mrs. Deng and Dr. Byra report support from Janssen Research & Development LLC during the conduct of the study and outside the submitted work and are employed by and shareholders of Johnson & Johnson. Dr. Mehra reports receiving travel support and consulting fees, paid to Brigham and Women's Hospital, from Abbott, fees for serving on a steering committee from Medtronic and Janssen (Johnson & Johnson), fees for serving on a data and safety monitoring board from Mesoblast, consulting fees from Portola, Bayer and Xogenex, and fees for serving as a scientific board member from NuPulseCV, Leviticus, and FineHeart. Dr. Neaton reports personal fees from Johnson & Johnson during the conduct of the study; fees from Janssen Research & Development LLC for serving as a member of the steering committee of the COMMANDER HF trial; and fees from Bristol-Myers Squibb and EBR Systems for serving on data and safety monitoring boards for heart failure trials. Dr. van Veldhuisen reports have received board membership fees from Johnson & Johnson during the conduct of this study. Dr. Greenberg reports consulting fees from Novartis, Janssen, Sanofi, Mesoblast, Zensun, Cellular Dynamics, MyoKardia, Bayer, Actelion, Viking, Amgen, Akcea, EBR System, IONIS and Tenaya. Dr. Spiro is employed by and a shareholder of Bayer. Dr. Zannad reports personal fees from Janssen, during the conduct of the study; personal fees from Novartis, fees from Bayer, Boston Scientific, Amgen, CVRx, Boehringer, AstraZeneca, Vifor Fresenius, Cardior, Cereno Pharmacuetical, Applied Therapeutics, Merck, other from CVCT and Cardiorenal. Remaining authors have no relationships with industry to disclose regarding this manuscript.

Abstract

Background: Heart failure (HF) trials selecting patients based on history of HF hospitalization alone are susceptible to regional variation in event rates. Elevated natriuretic peptides (NPs) as selection criteria may help HF ascertainment and risk enrichment. In the COMMANDER-HF trial, B-type natriuretic peptide (BNP)≥200ng/L or N-terminal pro-BNP ≥800ng/L were added to inclusion criteria as a mid-trial protocol amendment, providing a unique case-study of NP-based inclusion criteria.

Methods: We compared the baseline characteristics, event rates, and treatment effects for patients enrolled before/after NP protocol amendment. The primary endpoint was all-cause death, myocardial infarction, or stroke. Secondary endpoints included HF rehospitalization and cardiovascular death.

Results: A total of 5022 patients with LVEF ≤40% and coronary artery disease were included. Compared to patients enrolled before the NP protocol amendment, those enrolled post-amendment (n=3867, 77%) were older, and had more prevalent diabetes, lower BMI, LVEF and eGFR, higher heart rate and higher event rates: primary endpoint (HR 1.32, 95%CI 1.16-1.50), cardiovascular death (HR 1.29, 95%CI 1.11-1.50), HF rehospitalization (HR 1.31, 95%CI 1.15-1.49), and ISTH major bleeding (HR 1.71, 95% CI 1.11-2.65). Differences between pre- and post-amendment rates were confined to and driven by Eastern Europe. This protocol amendment did not modify the neutral effect of rivaroxaban on the primary endpoint (p-interaction=0.36) or secondary endpoints.

Conclusion: In a global event-driven trial of rivaroxaban in HF, requiring elevated NPs for inclusion increased event rates allowing earlier completion of the trial, but did not

modify treatment effect. These data inform future HF trials regarding the expected impact of NP-based inclusion criteria on patient characteristics and event rates.

Key Words: clinical trials; heart failure with reduced ejection fraction; cardiac biomarkers

Clinical Trials Registration: COMMANDER HF ClinicalTrials.gov identifier NCT01877915.

Abbreviations

BNP = B-type natriuretic peptide

COMMANDER HF = A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction, or Stroke in Participants with Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure

CI = confidence interval

CV = cardiovascular

HF = heart failure

HR = hazard ratio

ISTH = International Society on Thrombosis and Haemostasis

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

py = patient-years

Introduction

Careful definition of the study population is crucial for an efficient and generalizable clinical trial in heart failure (HF). Restricting enrollment to patients with rigorously defined HF who are at increased risk for endpoint events can increase the rate of events that are potentially modifiable, thereby increasing statistical power. Recent HF trials have used natriuretic peptide levels as inclusion criteria because they help to confirm the diagnosis of HF and are associated with increased event rates.(1-6)

In this analysis, we examine a case study in the effects of natriuretic peptide-based entry criteria on the clinical profile of the patients enrolled, event rates and study outcomes. COMMANDER HF (A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction, or Stroke in Participants with Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure) was a double-blind, randomized, placebo-controlled trial of low-dose rivaroxaban in patients recently admitted for decompensated HF.(7,8) At the beginning of the trial, decompensated HF was defined based on the site investigator's clinical assessment of the patient's HF symptoms and signs. After enrollment of 23% of patients, and because of the observation of a lower than expected blinded (pooled for 2 treatment groups) event rate, the protocol was amended to require N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration ≥800 ng per liter (L) or B-type natriuretic peptide (BNP) concentration ≥200 ng/L for enrollment. The purpose of the amendment was to prevent further enrollment of low risk patients who had not truly been hospitalized for decompensated HF, and thereby increase event rates and allow for more rapid completion of this event-driven trial. The addition of this amendment to the entry criteria

represents a unique opportunity to study the consequences of natriuretic peptide-based inclusion criteria while other inclusion criteria influencing enrollment are held constant.

Methods

Study Population & Clinical Endpoints

The study design of the COMMANDER HF trial has been previously described.(7,8) COMMANDER HF was an international, double-blind, randomized trial comparing the factor Xa inhibitor rivaroxaban and placebo. Key inclusion criteria included history of chronic HF for ≥3 months, treatment for decompensated HF in the previous 30 days, left ventricular ejection fraction (LVEF) ≤40%, history of coronary artery disease, and absence of atrial fibrillation or other indication for chronic anti-coagulation. Decompensated HF was defined by symptoms of worsening dyspnea or fatigue, objective signs of congestion, and/or adjustment of HF medications, requiring hospital admission or unscheduled parenteral diuretic.

Rivaroxaban dosed at 2.5mg twice daily did not reduce the incidence of the primary efficacy outcome, a composite of all-cause death, myocardial infarction, or stroke. Other efficacy endpoints included re-admission for worsening HF, cardiovascular (CV) and non-CV or unknown death, and components of the primary endpoint. Investigators reported outcomes on detailed case report forms, and the sponsor's clinical operations team verified the events using source data. Patients were followed until approximately 30 days after the global treatment end date, regardless of the date of enrollment. All subjects provided written informed consent. The protocol was approved by the appropriate institutional review board or ethics committee at each site.

Natriuretic Peptide Amendment

In May 2014, based on review of patient characteristics and the blinded event rate for 1155 patients, the Steering Committee amended the enrollment criteria to require a plasma NT-proBNP level ≥800ng/L or BNP level ≥200ng/L at any time between the index admission for decompensated HF and randomization.(8) Natriuretic peptide levels were measured by the individual site and were not verified by a core lab. Simultaneous with the amendment, enrollment in the Asia-Pacific region and several additional countries began. A total of 1440 patients were in countries that enrolled only after the protocol amendment; 3582 patients were in countries that enrolled both before and after the amendment. No countries enrolled only before the amendment.

Statistical Analysis

In this analysis, we compared baseline characteristics and crude event rates per 100 patient years for clinical outcomes in patients enrolled before and after the natriuretic peptide amendment. We described baseline characteristics using mean and standard deviation for normally distributed continuous variables, median and interquartile range for skewed continuous variables, and number and proportion for categorical variables. We compared these variables using F test, Chi-square test, Wilcoxon rank sum test, and Cochran-Mantel-Haenszel test as appropriate. We described time-to-first event outcomes using Kaplan-Meier estimates of cumulative risk and compared them between pre and post amendment groups using log rank test and Cox proportional hazards models with pre/post amendment as the only effect. The proportional hazards assumption was

evaluated by testing for significant trend in the change of hazard ratio over time and was not violated. Events rates before and after the protocol amendment were compared within regions, and heterogeneity in amendment effect by region was assessed through the interaction term for region and amendment using Cox models. We performed a sensitivity analysis excluding the Asia Pacific region and other countries that enrolled only after the protocol amendment, since differences in event rates in this population could be due opening enrollment at new sites rather than the amendment. In a second sensitivity analysis, follow-up for clinical events was limited to 2 years (all patients censored event-free at 2 years from randomization if still at risk), to address shorter follow-up duration in the post-amendment group. Two years was selected as the maximum duration in this analysis because 75% of patients in the post-amendment group had been censored or experienced primary endpoint events by that time. Heterogeneity caused by the amendment regarding to the treatment effect of rivaroxaban was evaluated through the interaction term for treatment and amendment using Cox models. A 2-sided p-value of <0.05 was considered significant. SAS version 9.4 (Cary, North Carolina) was used for statistical analysis.

Results

Baseline Characteristics

The baseline characteristics of patients enrolled after the amendment were consistent with greater risk. Post-amendment patients were older (67 years vs 65 years), with more prevalent diabetes (43% vs 34%) and anemia (34% vs 22%), higher heart rate (72 bpm vs 69 bpm) and lower systolic blood pressure (122 mmHg vs 124 mmHg) compared to

patients enrolled pre-amendment (**Table 1**). After the amendment, LVEF was lower (33% vs 36%), estimated glomerular filtration rate was lower (67 mL/min/1.73m^2 vs 71 mL/min/1.73m^2), and D-dimer was higher (380 µg/L vs 310 µg/L) compared to before the amendment. Rates of neurohormonal therapy were high in both groups, but slightly lower after the amendment. Cardiac devices were more common after the amendment (14% vs 9%). Conversely, fewer patients enrolled after the amendment were New York Heart Association functional class III or IV (51% vs 61%).

The regional distribution of patients shifted after the amendment. The majority of patients in both time periods were in Eastern Europe, but the percentage decreased from 89% before the amendment to 57% afterwards. Following the amendment, the proportions of North American, Latin American, and Western European patients increased. Asia Pacific enrollment began at time of the amendment.

Clinical Outcomes

Rates of key efficacy endpoints increased after the natriuretic peptide amendment. The primary efficacy endpoint, a composite of all-cause death, myocardial infarction, and stroke was more common after the amendment (15.46 vs 11.22 events per 100 patient-years[py], HR 1.32, 95% CI 1.16-1.50, p<0.001 using pre-amendment event rate as reference) (**Central Illustration & Table 2)**. A higher rate of all-cause mortality (12.84 vs 9.38 events/100py, HR 1.35, 95% CI 1.17-1.55, p<0.001) drove this difference. CV death (10.82 vs 7.91 events/100py, HR 1.29, 95% CI 1.11-1.50, p=0.001) and non-CV or unknown death (2.01 vs 1.48 events/100py, HR 1.70, 95% CI 1.18-2.45, p=0.004) were both more frequent after the amendment; relative risk was greater for non-CV or

unknown death, but absolute event rates for CV death were higher. Risk of rehospitalization for HF increased after the amendment (20.74 vs 11.82 events/100py, HR 1.31, 95% CI 1.15-1.49, p<0.001).

The increase in primary endpoint event rate after the protocol amendment was driven by and confined to Eastern Europe **(Table 3)**. Eastern European sites enrolled 89% of patients before the protocol amendment and 57% afterwards. Eastern Europe had the lowest event rate of any region both before and after the amendment. In Eastern Europe, the amendment increased the primary endpoint event rate by 35% (13.64 events/100py post-amendment vs 10.11 events/100py pre-amendment, HR 1.33, 95% CI 1.14-1.56). Comparison of event rates pre/post amendment in other regions was limited as >93% of patients in these regions were enrolled post-amendment; however, there was no signal for an increase in event rate. Similar regional differences in event rates were observed for other efficacy outcomes.

Bleeding rates were overall low but increased after the amendment (**Table 4)**. There was a trend toward increased rate of the primary safety endpoint—a composite of fatal bleeding or bleeding into a critical space with a potential for causing permanent disability—that did not reach statistical significance (0.61 vs 0.32 events/100py, HR 1.51, 95% CI 0.71-3.20, p=0.28). International Society on Thrombosis and Haemostasis (ISTH) major bleeding (2.10 events/100py post-amendment vs 0.86 events/100py pre-amendment, HR 1.71, 95% CI 1.11-2.65, p=0.02), bleeding in a critical space with potential permanent disability (0.56 vs 0.16 events/100py, HR 3.01, 95% CI 1.10-8.26, p=0.03) and ISTH bleeding at a critical site (0.84 vs 0.19 events/100py, HR 3.79, 95% CI 1.54-9.33, p<0.01) occurred more frequently in post-amendment patients.

Sensitivity Analyses

To address the possibility that opening enrollment in Asia Pacific and other countries after the amendment caused the changes in event rates, we performed a sensitivity analysis excluding these countries (**Supplemental Table 1)**. This sub-population included 3582 patients: all 1155 patients enrolled pre-amendment and 2427 patients enrolled post-amendment. A similar pattern of results was observed as in the full population, though with less statistical power. The increased risk of the primary efficacy endpoint (HR 1.23, 95% CI 1.07-1.42, $p<0.01$) and CV death (1.28, 95% CI 1.09-1.51, $p<0.01$) retained statistical significance in this population. The differences in non-CV or unknown death (HR 1.41, 95% CI 0.93-2.12, $p=0.10$) and rehospitalization for HF (HR 1.10, 95% CI 0.96-1.26, $p=0.19$) did not reach statistical significance. Differences in bleeding endpoints were directionally consistent but no longer statistically significant.

A second sensitivity analysis restricted follow-up to the first 2 years following randomization, in order to balance the duration of follow-up between the pre- and post-amendment groups. Because all patients were followed until the global trial end date regardless of randomization date, median follow-up was longer in the pre-amendment group (3.6 years pre-amendment vs 1.4 years post-amendment). The results of this sensitivity analysis were similar to the main trial population (**Supplemental Table 2**).

Treatment Group Interaction

Enrollment before or after the natriuretic peptide amendment did not modify the null relationship between rivaroxaban and the primary efficacy endpoint (p-interaction=0.36)

or any other endpoints (**Table 5**). The hazard ratio of rivaroxaban for the primary efficacy endpoint was 1.02 (0.84-1.24) before the amendment and 0.91 (0.80-1.04) after the amendment.

Discussion

In a global clinical trial of low-dose rivaroxaban in patients recently treated for decompensated HF with sinus rhythm, reduced LVEF, and underlying coronary artery disease, we studied the impact of a protocol amendment requiring elevated natriuretic peptide level for inclusion. This amendment was mandated by the lower than expected event rate after enrollment of almost 25% of the targeted number of patients, and the suspicion that including patients based on history of recent admission alone may have led to enrolling patients with heterogenous risk. The amendment resulted in (1) enrollment of patients with more comorbidities, (2) ~30% higher rates of the primary endpoint (death, MI or stroke) driven by Eastern European sites and (3) higher rates of rehospitalization for HF, bleeding, and death (both CV and non-CV). Despite the amendment, no difference in rivaroxaban treatment effect was observed. Our results support the use of natriuretic peptide-based inclusion criteria in future HF trials to enrich events, especially in trials where HF is mainly ascertained by a history of HF hospitalization. Bleeding and non-CV death rates should be considered when selecting natriuretic peptide thresholds, as higher thresholds may alter the benefit-to-harm trade-off and increase the risk for competing events. (9,10)

The concordant increases in baseline risk profile and event rates were consistent with our hypothesis that the protocol amendment prevented a subgroup of lower risk

patients from Eastern Europe from enrolling. Baseline factors traditionally associated with poor prognosis, including older age, lower LVEF, and renal dysfunction, were more common after the amendment. One discordant variable was site-determined New York Heart Association functional class, which was lower after the amendment (i.e. fewer patients were attributed functional class III or IV after the amendment). The distinction between functional classes II and III is subjective and could have been subjectively inflated by investigators in the pre-amendment group to justify trial enrollment. A similar pattern in the baseline characteristics was found in the TOPCAT trial, despite including a very different population; patients enrolled by natriuretic peptide-based criteria were older, with lower potassium and eGFR, compared to those enrolled based on hospitalization alone. (11)

We chose not to control for baseline characteristics because changes in baseline characteristics are on the causal pathway between the inclusion criteria and events. We were, however, concerned that opening of enrollment in Asia Pacific and other countries after the amendment could have confounded our results, because patients in these areas have been shown to present major differences in characteristics and events compared to patients in other geographical areas.(12) However, a sensitivity analysis excluding these countries/regions showed a slightly smaller but still significant increase in event rates after the amendment. Moreover, regional analysis shows that a higher event rate within the largest region, Eastern Europe, drove the changes. It is likely that both the natriuretic peptide protocol amendment and addition of new regions with high event rates contributed to the increase in event rates. But, using the sensitivity analysis, we were able to isolate the distinct effect of the NP amendment. Our findings are consistent with and

build upon prior work demonstrating that natriuretic peptides are markers of HF risk.(4,13) Age-based cutoffs (NT-proBNP 450, 900, and 1800 ng/L for ages <50, 50-75, and >75, respectively) demonstrate 90% sensitivity and 84% specificity for the diagnosis acute HF.(2) Once HF has been diagnosed, higher natriuretic peptide levels predict adverse events.(3,14) Among patients enrolled in COMMANDER HF with available natriuretic peptide values, patients in the highest quartile had nearly double the event rate of those in the lowest quartile.(8) The protocol amendment described in this study provides a unique case study that isolates the effect of natriuretic peptide-based inclusion criteria while other trial-level factors were held constant. Requiring elevated natriuretic peptides for enrollment enriched event rates despite a background of other high-risk features: recent decompensated HF, reduced LVEF, and history of coronary artery disease.

The 32% increase in primary endpoint event rate after the natriuretic peptide protocol amendment allowed more rapid completion of this event driven trial. A total of 1284 primary endpoint events occurred in 5022 patients during the trial. Assuming stable event rates over time and similar duration of follow-up, if the amendment had not been made, the trial would have needed to recruit an additional one thousand patients for a total of 6016. On the other hand, had original protocol required elevated natriuretic peptides, only 4366 patients would have been required. However, improved efficiency must be balanced against the risk of enrolling patients with more advanced disease whose clinical course is not modified by the study drug. Observed increases in rates of bleeding and non-cardiovascular death after the protocol amendment demonstrate that non-modifiable events are also more common in patients with high natriuretic peptides. Prior

research has found that elevated troponin identifies patients at greater risk for specifically CV death, while elevated NT-proBNP is associated with both CV and non-CV death rates. (15) Other contemporary clinical trials in HF with reduced ejection fraction have adopted natriuretic peptide-based inclusion criteria, with varying cutoffs depending on the target population. In chronic HF, the DAPA-HF trial required NT-proBNP ≥600ng/L for most patients, with a lower threshold (≥400ng/L) for patients hospitalized for HF within 12 months and a higher threshold (≥900ng/L) for patients in atrial fibrillation.(6) Patients in atrial fibrillation have higher levels of NT-proBNP independent of HF severity.(16,17) The PIONEER-HF trial, which enrolled decompensated HF patients, required higher levels: NT-proBNP >1600ng/L or BNP>800ng/L.(5) In our study, a threshold of NT-proBNP≥800ng/L, though lower than average levels in decompensated HF which exceed 4000ng/L, was sufficient to enrich the population.(2) A lower threshold for obese patients could be considered since natriuretic peptide levels are lower in obese patients for similar HF severity.

We found that natriuretic peptide-based inclusion criteria were particularly important in Eastern Europe, a region which offers rapid enrollment but has suffered from low event rates and inconsistent application of inclusion criteria in other HF trials.(18,19) The TOPCAT trial, which included patients with HF and preserved ejection fraction, a population in which diagnosis is more subjective, exemplifies this issue. Patients from Russia and Georgia were more likely to be enrolled by hospitalization criteria alone rather than elevated natriuretic peptide level, and experienced similar event rates to the general population of those countries and one quarter as many primary endpoint events as those in the Americas.(20) In COMMANDER HF, the large

proportion of patients enrolling in Eastern Europe, and their low event rate, contributed to the decision to implement the natriuretic-peptide protocol amendment. The amendment likely prevented the further enrollment of Eastern European patients whose index hospitalization was not truly for worsening HF. Our findings demonstrate the utility of objective inclusion criteria such as natriuretic peptides, especially in regions where the patient characteristics, treatments, and access to care may be very different.

Our analysis has several limitations. First, as in any study comparing outcomes before and after an intervention, it is possible that other changes were responsible for the observed differences in event rates. As described, a sensitivity analysis excluding countries in which enrollment opened at or after the amendment yielded consistent results. Second, follow-up was by necessity shorter for patients enrolled after the amendment, since all patients who did not experience events were censored on the global treatment end date of this event-driven trial. However, a sensitivity analysis in which all patients were censored 2 years after randomization showed consistent results. Third, natriuretic peptide levels were measured by the individual sites, not a core lab, which could have introduced inaccuracy. However, use of readily available, site-reported values reduces cost and avoids the need to ship samples to a central lab or provide sites with point of care assays. Fourth, assessment of rivaroxaban treatment benefit in appropriate patients enrolled after the natriuretic-peptide amendment was underpowered, since the power calculation was performed on the whole population.

Conclusion

In a global trial of rivaroxaban in heart failure with reduced LVEF, a protocol amendment requiring elevated natriuretic peptide level for inclusion increased event rates (including bleeding and non-CV death), but did not modify treatment effect. These data may inform future HF trials regarding the expected impact of NP-based inclusion criteria on patient characteristics and event rates, including potentially modifiable and adverse events.

Clinical Perspective:

In a global trial of rivaroxaban in patients with heart failure, systolic dysfunction, and coronary artery disease, a protocol amendment requiring elevated natriuretic peptides for inclusion increased event rates for the primary endpoint (death, myocardial infarction, or stroke), and other endpoints including cardiovascular death, rehospitalization for heart failure, and bleeding. The change in inclusion criteria did not modify the neutral treatment effect of rivaroxaban.

Translational Outlook:

These results inform future heart failure trials regarding the expected impact of natriuretic peptide-based inclusion criteria on patient characteristics and event rates.

References

1. Vodovar N, Mebazaa A, Januzzi JL, Jr. et al. Evolution of natriuretic peptide biomarkers in heart failure: Implications for clinical care and clinical trials. International Journal of Cardiology 2018;254:215-221.
2. Januzzi JL, van Kimmenade R, Lainchbury J et al. NT-proBNP testing for diagnosis and short-term prognosis in acute destabilized heart failure: an international pooled analysis of 1256 patients: The International Collaborative of NT-proBNP Study. European heart journal 2005;27:330-337.
3. Anand IS, Fisher LD, Chiang Y-T et al. Changes in Brain Natriuretic Peptide and Norepinephrine Over Time and Mortality and Morbidity in the Valsartan Heart Failure Trial (Val-HeFT). Circulation 2003;107:1278-1283.
4. Volpe M, Rubattu S, Burnett J, Jr. Natriuretic peptides in cardiovascular diseases: current use and perspectives. European heart journal 2013;35:419-425.
5. Velazquez EJ, Morrow DA, DeVore AD et al. Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure. New Engl J Med 2018;380:539-548.
6. McMurray JJV, Solomon SD, Inzucchi SE et al. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. New Engl J Med 2019.
7. Zannad F, Greenberg B, Cleland JGF et al. Rationale and design of a randomized, double-blind, event-driven, multicentre study comparing the efficacy and safety of oral rivaroxaban with placebo for reducing the risk of death, myocardial infarction or stroke in subjects with heart failure and significant coronary artery disease following an exacerbation of heart failure: the COMMANDER HF trial. European Journal of Heart Failure 2015;17:735-742.
8. Zannad F, Anker SD, Byra WM et al. Rivaroxaban in Patients with Heart Failure, Sinus Rhythm, and Coronary Disease. New Engl J Med 2018;379:1332-1342.
9. Voors AA. Sense and Sensibility of the Use of NT-proBNP for Eligibility in Clinical Trials. JACC: Heart Failure 2018;6:257-259.
10. Savarese G, Orsini N, Hage C et al. Utilizing NT-proBNP for Eligibility and Enrichment in Trials in HFpEF, HFmrEF, and HFrEF. JACC: Heart Failure 2018;6:246-256.
11. Pitt B, Pfeffer MA, Assmann SF et al. Spironolactone for heart failure with preserved ejection fraction. N Engl J Med 2014;370:1383-92.
12. Dewan P, Jhund PS, Shen L et al. Heart failure with reduced ejection fraction: comparison of patient characteristics and clinical outcomes within Asia and between Asia, Europe and the Americas. European journal of heart failure 2019;21:577-587.
13. Ferreira JP, Duarte K, Graves TL et al. Natriuretic Peptides, 6-Min Walk Test, and Quality-of-Life Questionnaires as Clinically Meaningful Endpoints in HF Trials. Journal of the American College of Cardiology 2016;68:2690-2707.
14. Bettencourt P, Azevedo A, Pimenta J, Friões F, Ferreira S, Ferreira A. N-Terminal–Pro-Brain Natriuretic Peptide Predicts Outcome After

Hospital Discharge in Heart Failure Patients. Circulation 2004;110:2168-2174.
15. Ferreira JP, Ouwerkerk W, Tromp J et al. Cardiovascular and non-cardiovascular death distinction: the utility of troponin beyond N-terminal pro-B-type natriuretic peptide. Findings from the BIOSTAT-CHF study. European Journal of Heart Failure;n/a.
16. Cikes M, Claggett B, Shah AM et al. Atrial Fibrillation in Heart Failure With Preserved Ejection Fraction. The TOPCAT Trial 2018;6:689-697.
17. Kristensen SL, Jhund PS, Mogensen UM et al. Prognostic Value of N-Terminal Pro-B-Type Natriuretic Peptide Levels in Heart Failure Patients With and Without Atrial Fibrillation. Circulation: Heart Failure 2017;10:e004409.
18. Ferreira JP, Girerd N, Rossignol P, Zannad F. Geographic differences in heart failure trials. European Journal of Heart Failure 2015;17:893-905.
19. Tromp J, Ferreira JP, Janwanishstaporn S et al. Heart failure around the world. European Journal of Heart Failure;0.
20. Pfeffer MA, Claggett B, Assmann SF et al. Regional Variation in Patients and Outcomes in the Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist (TOPCAT) Trial. Circulation 2015;131:34-42.

Central Illustration: Kaplan-Meier Curves for Efficacy Endpoints, According to Pre/Post Natriuretic Peptide Amendment Enrollment

Hazard ratios (95% confidence interval) are from a Cox proportional hazards model with pre/post amendment as the only effect. P-values (two-sided) are from the log-rank test. CV, cardiovascular; HF, heart failure; MI, myocardial infarction.

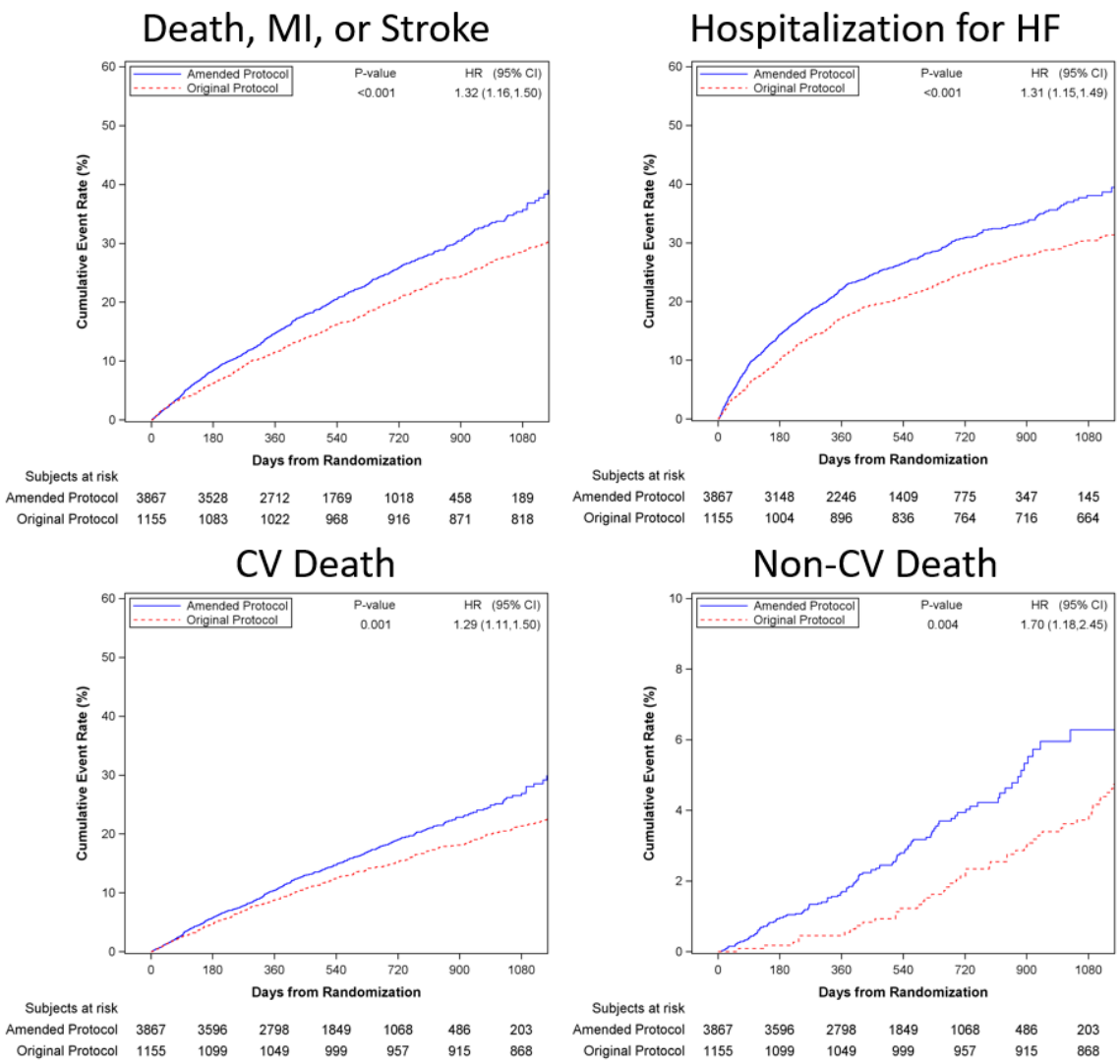

Table 1: Baseline Characteristics of Patients Enrolled Before & After Natriuretic Peptide Amendment

1. Data are presented as mean (standard deviation) for continuous variables, median (interquartile range) for highly skewed continuous variables, and number (percentage of total) for categorical variables.

2. p-values (two-sided) for characteristics with continuous values are from the F-test; p-values (two-sided) for characteristics with categorical values are from the Chi-Square test; p-values (two-sided) for variables with ordinal values are from the Cochran-Mantel-Haenszel test; p-values (two-sided) for D-Dimer Troponin I and Troponin T, and Baseline Ejection Fraction are from Wilcoxon Test.

3. Percentages for characteristics with categorical values and statistics summaries for characteristics with continuous values are based on number of subjects with non-missing values in each pre/post amendment group.

4. The following characteristics have limited amount of observations: D-Dimer was from 4107 subjects, Troponin I 604 subjects, and Troponin T 497 subjects.

[a] Anemia defined as Hgb <13 g/dl in men and <12 g/dl in women.

[b] Cardiac devices include implantable cardiac defibrillator, pacemaker, and cardiac resynchronization therapy.

Characteristic	**Before Amendment (n=1155, 23%)**	**After Amendment (n=3867, 77%)**	**p-value**
Age (years)	64.7 (9.7)	66.9 (10.3)	<0.001
Women	242 (21%)	908 (24%)	0.073
Race			<0.001
White	1139 (99%)	2989 (77%)	
Black or African American	6 (1%)	59 (2%)	

Asian	0	727 (19%)	
Other	10 (1%)	92 (2%)	
Region			<0.001
Eastern Europe	1032 (89%)	2192 (57%)	
North America	15 (1%)	134 (4%)	
Asia Pacific	0	733 (19%)	
Latin America	45 (4%)	413 (11%)	
Western Europe and South Africa	63 (6%)	395 (10%)	
New York Heart Association classification			<0.001
I	16 (1%)	133 (3%)	
II	437 (38%)	1781 (46%)	
III	687 (60%)	1775 (46%)	
IV	14 (1%)	178 (5%)	
Medical history			
MI	1014 (88%)	2789 (72%)	<0.001
Stroke	87 (8%)	366 (10%)	0.044
Diabetes	397 (34%)	1655 (43%)	<0.001
Insulin use	76 (7%)	449 (12)	<0.001
Hypertension	928 (80%)	2855 (74%)	<0.001
Anemia [a]	248 (22%)	1294 (34%)	<0.001
Body mass index (kg/m^2)	28.6 (4.9)	27.4 (5.2)	<0.001
Systolic blood pressure (mmHg)	123.6 (13.5)	122.5 (15.9)	0.035
Diastolic blood pressure (mmHg)	74.7 (8.7)	72.9 (9.9)	<0.001
Heart rate (bpm)	69.4 (9.7)	71.7 (10.9)	<0.001
Ejection fraction (%), median (IQR)	36 (30, 39)	33 (27, 38)	<0.001
eGFR ($mL/min/1.73\ m^2$)	71.0 (24.1)	67.2 (23.2)	<0.001
Hemoglobin (g/dL)	13.9 (1.7)	13.4 (1.8)	<0.001
Troponin I (ng/ml), median (IQR) (n=604)	0.05 (0.04, 0.11)	0.04 (0.02, 0.20)	0.847
Troponin T (ng/ml), median (IQR) (n=497)	0.03 (0.01, 0.06)	0.04 (0.02, 0.16)	0.053
D-dimer (ug/L), median (IQR) (n=4107)	310 (190, 545)	380 (225, 695)	<0.001
Medical therapy at baseline			
Diuretic	1154 (100%)	3845 (99%)	0.033
Beta blocker	1096 (95%)	3546 (92%)	<0.001

Angiotensin-converting enzyme inhibitor or angiotensin receptor blocker use	1120 (97%)	3540 (92%)	<0.001
Angiotensin receptor-neprilysin inhibitor	0	41 (1%)	<0.001
Mineralocorticoid receptor antagonist	916 (79%)	2924 (76%)	0.009
Nitrate	293 (25%)	715 (19)	<0.001
Hydralazine	8 (1%)	47 (1%)	0.134
Digoxin	71 (6%)	362 (9%)	<0.001
Aspirin vs. dual antiplatelet use			<0.001
Aspirin alone	765 (66%)	2164 (56%)	
Thienopyridine alone	34 (3%)	235 (6%)	
Dual antiplatelet therapy	350 (30%)	1396 (36%)	
None	6 (1%)	72 (2%)	
Cardiac device [b]	107 (9%)	554 (14%)	<0.001

Table 2: Efficacy Outcomes Before & After Natriuretic Peptide Amendment

Hazard ratios were calculated using a Cox proportional hazard model with pre/post amendment as the only effect. P-values are from log-rank test. CI, confidence interval; CV, cardiovascular; HF, heart failure.

	Before Amendment Event Rate/ (100 pt-yr) (n=1155, 23%)	**After Amendment Event Rate/ (100 pt-yr) (n=3867, 77%)**	**Hazard Ratio (95% CI), After vs Before**	**P-value**
Composite primary efficacy outcome	11.22	15.46	1.32 (1.16, 1.50)	<0.001
Death from any cause	9.38	12.84	1.35 (1.17, 1.55)	<0.001
Myocardial infarction	2.04	2.46	1.08 (0.79, 1.47)	0.645
Stroke	1.25	1.40	0.92 (0.63, 1.37)	0.693
CV death or Hospitalization for HF	16.97	27.34	1.26 (1.13, 1.40)	<0.001
CV death	7.91	10.82	1.29 (1.11, 1.50)	0.001
Non-CV or unknown death	1.48	2.01	1.70 (1.18, 2.45)	0.004
Hospitalization for HF	11.82	20.74	1.31 (1.15, 1.49)	<0.001
Hospitalization for non-HF CV Cause	10.83	15.37	1.13 (0.99, 1.30)	0.071
All-cause mortality or Hospitalization for HF	17.89	28.90	1.29 (1.16, 1.44)	<0.001

Table 3: Regional Differences in Natriuretic Peptide Amendment Effect on the Primary Endpoint

Hazard ratios were calculated using a Cox proportional hazard model with pre/post amendment as the only effect. P-value for interaction between region and natriuretic peptide amendment was 0.003. Latin America and Asia Pacific were grouped together since no patients were enrolled in Asia Pacific before the amendment. CI, confidence interval.

	Before Amendment		**After Amendment**		
	No. of Patients	**Event Rate/ (100 pt-yr)**	**No. of Patients**	**Event Rate/ (100 pt-yr)**	**Hazard Ratio (95% CI), After vs Before**
Eastern Europe	1032	10.11	2192	13.64	1.33 (1.14-1.56)
North America	15	16.07	134	14.26	0.92 (0.38-2.19)
Latin America & Asia Pacific	45	26.64	1146	18.09	0.63 (0.42-0.96)
Western Europe & S. Africa	63	23.26	395	19.15	0.71 (0.47-1.06)

Table 4: Safety Outcomes Before & After Natriuretic Peptide Amendment

Hazard ratios were calculated using a Cox proportional hazard model with pre/post amendment as the only effect. P-values are from log-rank test. CI, confidence interval; Hgb, hemoglobin; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis.

	Before Amendment Events / (100 pt-yr) (n=1155, 23%)	**After Amendment Events / (100 pt-yr) (n=3867, 77%)**	**HR (95% CI), After vs Before**	**P-value**
Composite primary safety outcome	0.32	0.61	1.51 (0.71, 3.20)	0.280
Fatal bleeding	0.22	0.22	0.62 (0.24, 1.61)	0.318
Bleeding in critical space with potential for permanent disability	0.16	0.56	3.01 (1.10, 8.26)	0.026
ISTH major bleeding	0.86	2.10	1.71 (1.11, 2.65)	0.015
ISTH bleeding with Hgb decrease ≥2g/dL	0.60	1.32	1.40 (0.83, 2.36)	0.201
ISTH bleeding requiring transfusion ≥2 Units	0.35	0.76	1.29 (0.66, 2.55)	0.456
ISTH bleeding at critical sites	0.19	0.84	3.79 (1.54, 9.33)	0.002
ISTH fatal bleeding	0.13	0.12	0.52 (0.15, 1.86)	0.308
Bleeding requiring hospitalization	0.73	1.72	1.67 (1.03, 2.69)	0.034

Table 5: Treatment Effects of Rivaroxaban vs Placebo on Efficacy and Safety Outcomes Before & After Natriuretic Peptide Amendment

1. Hazard ratios and 95% confidence intervals are from a Cox proportional hazards model with treatment assignment as the only effect.

2. P-values (two-sided) for the interaction of treatment assignment and pre/post amendment are based on the Cox proportional hazard model. Covariates included in the Cox model are treatment assignment, pre/post amendment and interaction term for treatment and pre/post amendment.

CV, cardiovascular; HF, heart failure; Hgb, hemoglobin; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis.

	HR (95% CI) Before Amendment (n=1155, 23%)	**HR (95% CI) After Amendment (n=3867, 77%)**	**Interaction p-value**
Composite primary efficacy outcome	1.02 (0.84, 1.24)	0.91 (0.80, 1.04)	0.355
Death from any cause	1.07 (0.86, 1.32)	0.95 (0.82, 1.09)	0.357
Myocardial infarction	0.77 (0.49, 1.23)	0.86 (0.62, 1.19)	0.724
Stroke	0.65 (0.36, 1.19)	0.67 (0.43, 1.05)	0.939
CV death or Hospitalization for HF	0.99 (0.84, 1.18)	1.00 (0.90, 1.11)	0.967
CV death	1.01 (0.80, 1.27)	0.93 (0.79, 1.08)	0.545
Non-CV or unknown death	1.44 (0.83, 2.47)	1.06 (0.74, 1.51)	0.356
Hospitalization for HF	1.01 (0.82, 1.24)	0.99 (0.87, 1.11)	0.855
Hospitalization for non-HF CV cause	0.99 (0.80, 1.23)	0.93 (0.81, 1.07)	0.637
All-cause mortality or hospitalization for HF	1.04 (0.88, 1.23)	1.00 (0.91, 1.11)	0.740
Composite primary safety outcome	1.50 (0.42, 5.33)	0.65 (0.32, 1.35)	0.260
Fatal bleeding	1.33 (0.30, 5.96)	0.86 (0.26, 2.82)	0.650
Bleeding in critical space with potential for permanent disability	0.67 (0.11, 4.01)	0.67 (0.31, 1.43)	0.998
ISTH major bleeding	2.01 (0.90, 4.48)	1.62 (1.09, 2.39)	0.629

ISTH bleeding with Hgb decrease ≥2g/dL	3.77 (1.25, 11.35)	1.59 (0.97, 2.60)	0.161
ISTH bleeding requiring transfusion ≥2 Units	1.75 (0.51, 5.96)	1.76 (0.91, 3.40)	0.988
ISTH bleeding at critical sites	0.50 (0.09, 2.74)	1.25 (0.68, 2.30)	0.319
ISTH fatal bleeding	0.33 (0.03, 3.19)	0.52 (0.09, 2.81)	0.762
Bleeding requiring hospitalization	2.30 (0.95, 5.58)	1.13 (0.74, 1.72)	0.157

Supplemental Table 1: Sensitivity Analysis: Rates of Efficacy and Safety Endpoints Before & After Protocol Amendment Excluding Countries Enrolling Only After Amendment

The eighteen countries excluded from this analysis due to enrolling only after the protocol amendment are: Australia, China, Japan, South Korea, Malaysia, Lithuania, Latvia, Slovakia, Turkey, Brazil, Denmark, France, United Kingdom, Greece, Italy, Portugal, Sweden, and South Africa. Hazard ratios were calculated using a Cox proportional hazard model with pre/post amendment as the only effect. P-values are from the log-rank test.

CV, cardiovascular; HF, heart failure; Hgb, hemoglobin; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis.

	Before Amendment Events / 100 pt-yr (n=1155, 32%)	**After Amendment Events / 100 pt-yr (n=2427, 68%)**	**HR (95% CI)**	**P-value**
Composite primary efficacy outcome	11.22	14.19	1.23 (1.07, 1.42)	0.004
Death from any cause	9.38	12.16	1.30 (1.12, 1.51)	<0.001
Myocardial infarction	2.04	2.28	1.00 (0.72, 1.41)	0.982
Stroke	1.25	1.15	0.79 (0.51, 1.22)	0.287
CV death or Hospitalization for HF	16.97	23.37	1.11 (0.99, 1.25)	0.072
CV death	7.91	10.58	1.28 (1.09, 1.51)	0.003

Non-CV or unknown death	1.48	1.58	1.41 (0.93, 2.12)	0.102
Hospitalization for HF	11.82	16.80	1.10 (0.96, 1.26)	0.188
Hospitalization for non-HF CV cause	10.83	14.22	1.08 (0.93, 1.26)	0.285
All-cause mortality or hospitalization for HF	17.89	24.55	1.14 (1.01, 1.28)	0.030
Composite primary safety outcome	0.32	0.44	1.09 (0.47, 2.51)	0.845
Fatal bleeding	0.22	0.24	0.69 (0.25, 1.92)	0.474
Bleeding in critical space with potential for permanent disability	0.16	0.38	2.10 (0.70, 6.30)	0.180
ISTH major bleeding	0.86	1.64	1.36 (0.85, 2.19)	0.200
ISTH bleeding with Hgb decrease ≥2g/dL	0.60	1.13	1.24 (0.71, 2.17)	0.458
ISTH bleeding requiring transfusion ≥2 Units	0.35	0.50	0.91 (0.42, 1.96)	0.813
ISTH bleeding at critical sites	0.19	0.47	2.32 (0.85, 6.35)	0.095
ISTH fatal bleeding	0.13	0.15	0.67 (0.18, 2.50)	0.547
Bleeding requiring hospitalization	0.73	1.42	1.40 (0.83, 2.34)	0.201

Supplemental Table 2: Sensitivity Analysis: Rates of Efficacy and Safety Endpoints Before & After Protocol Amendment, Limited to First 2 Years of Follow-Up.

Patients who remained at risk 2 years after randomization were censored event-free at 2 years. Hazard ratios were calculated using a Cox proportional hazard model with pre/post amendment as the only effect. P-values are from the log-rank test.

CV, cardiovascular; HF, heart failure; Hgb, hemoglobin; HR, hazard ratio; ISTH, International Society on Thrombosis and Haemostasis.

	Before Amendment Event Rate/ (100 pt-yr) (n=1155, 23%)	**After Amendment Event Rate/ (100 pt-yr) (n=3867, 77%)**	**Hazard Ratio (95% CI), After vs Before**	**P-value**
Composite primary efficacy outcome	11.90	15.58	1.29 (1.12, 1.49)	<0.001
Death from any cause	9.63	12.86	1.33 (1.13, 1.56)	<0.001
Myocardial infarction	2.41	2.43	0.94 (0.67, 1.30)	0.691
Stroke	1.59	1.47	0.91 (0.61, 1.38)	0.669
CV death or Hospitalization for HF	20.75	28.42	1.26 (1.12, 1.41)	<0.001
CV death	8.48	10.89	1.26 (1.06, 1.49)	0.007
Non-CV death	1.14	1.96	1.86 (1.19, 2.90)	0.006
Hospitalization for HF	14.98	21.69	1.31 (1.14, 1.50)	<0.001
Hospitalization for non-HF CV cause	12.83	15.96	1.16 (1.00, 1.34)	0.046

All-cause mortality or hospitalization for HF	21.46	29.99	1.29 (1.15, 1.45)	<0.001
Composite primary safety outcome	0.48	0.60	1.20 (0.56, 2.57)	0.631
Fatal bleeding	0.37	0.24	0.62 (0.24, 1.61)	0.318
Bleeding in critical space with potential for permanent disability	0.21	0.54	2.35 (0.81, 6.79)	0.104
ISTH major bleeding	1.28	2.11	1.49 (0.95, 2.34)	0.079
ISTH bleeding with Hgb decrease ≥2g/dL	0.96	1.34	1.27 (0.75, 2.15)	0.382
ISTH bleeding requiring transfusion ≥2 Units	0.53	0.82	1.38 (0.68, 2.77)	0.368
ISTH bleeding at critical sites	0.21	0.82	3.52 (1.25, 9.90)	0.011
ISTH fatal bleeding	0.21	0.13	0.52 (0.15, 1.86)	0.308
Bleeding requiring hospitalization	1.01	1.71	1.50 (0.91, 2.48)	0.111